IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AFFYMETRIX, INC., a Delaware corporation, Plaintiff/Counter-Defendant, v. **ILLUMINA, INC.**, a Delaware corporation, Defendant/Counter-Plaintiff.	Civil Action No.: 04-901 JJF **PUBLIC VERSION**

ILLUMINA, INC.'S OPENING *MARKMAN* BRIEF

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Illumina respectfully submits this claim construction brief to address the disputed terms of the five patents now asserted by Affymetrix. Illumina's proposed constructions are based on the strict application of the claim construction principles set forth by the Federal Circuit in its *en banc* opinion in *Phillips v. AWH Corp.*

Affymetrix, in contrast, seeks claim constructions largely divorced from the intrinsic record, including the actual claim language, the discussion in the specification of the patents (which describes what the inventors purportedly invented), and its statements to the Patent Office that were necessary to obtain the claims-in-suit. Affymetrix's proposed claim constructions in many instances seek to introduce or perpetuate, not resolve or clarify, ambiguities in the claims. The Federal Circuit has instructed district courts to reject such invitations to cast a jury adrift with ambiguous claims and claim terms:

> [T]he district court normally will need to provide the jury in a patent case with instructions adequate to ensure that the jury fully understands the court's claim construction rulings and what the patentee covered by the claims. . . . This means that, as to claim coverage, the district court must instruct the jury on the meanings to be attributed to all disputed terms used in the claims in suit so that the jury will be able to "intelligently determine the questions presented."

Sulzer Textil A.G. v. Picanol N.V., 358 F.3d 1356, 1366 (Fed. Cir. 2004) (citations omitted). Affymetrix's case depends on seeking ambiguous non-constructions that obscure what it purportedly invented, and then trying to capitalize on these ambiguities in applying the claims against Illumina's products. Illumina's constructions stay true to the intrinsic evidence and should be adopted.

I. TECHNOLOGY BACKGROUND

The asserted claims of the five patents-in-suit generally relate to the technology of nucleic acid hybridization experiments and, in many instances, nucleic acid microarrays. While Illumina understands that the Court has been previously exposed to aspects of this technology in the case of *Oxford Gene Technology Ltd. v. Affymetrix, Inc.*, Civil Action No. 99-348-JJF, it first provides a refresher of this technology. Illumina will then provide a very brief description of each sub-area of

the technology that is implicated by each of the patents-in-suit. Finally, Illumina will briefly describe its own technology to provide some context to the claim construction disputes.

A. General Technology Background

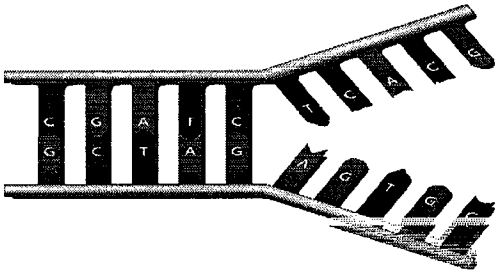
DNA provides the information necessary for cells to reproduce and to produce specific proteins critical to sustaining life. On the molecular level, DNA consists of two long chains or strands that wrap around each other in a shape typically referred to as a "double helix." Each strand of DNA is formed of building blocks called "nucleotides." Each nucleotide consists of a sugar group, a phosphate group and a base. The sugar and phosphate groups in each of the nucleotides in a DNA strand in nature are the same — it is the bases in the nucleotide building blocks that can differ.

The two strands of the double helix form a structure that visually resembles a twisted ladder. Each strand forms one side of the ladder. The sugar and phosphate groups in the nucleotides form the sides of the ladder. The sides of the ladder are connected by rungs made up of pairs of bases, one from each of the two DNA strands that have come together to form the ladder. Four different bases — adenine ("A"), guanine ("G"), cytosine ("C") and thymine ("T") — occur naturally in DNA and are sometimes referred to as "natural" bases. A particular DNA molecule can be graphically represented by listing in order the nucleotides in that DNA molecule, *e.g.*, A-T-G-C-C-G-T-A. It is the order or sequence of the bases, and therefore the order or sequence of the nucleotides, in a particular strand of DNA that carries genetic information.

The process by which two strands of DNA can come together to form a double stranded structure is called "hybridization." This process can be envisioned as the closing of a zipper. If the sequence of bases in two strands of DNA match closely enough, the two strands can bind together through this hybridization process to form the double stranded ladder. Due to a nucleotide's chemical structure, each has a "complementary" nucleotide with which it will preferentially form a

base pair rung in the ladder structure. Thus, in nature, an A nucleotide preferentially pairs with T,[1] and C with G. Because nucleotides preferentially bind with complementary nucleotides, a particular strand of DNA will hybridize best with a strand that has a fully complementary sequence.

Figure of DNA Hybridization



In a hybridization experiment, the known piece of DNA is typically referred to as a "probe" while the unknown, sample DNA to be analyzed is typically referred to as a "target." Because a probe will preferentially hybridize to a complementary sequence in a target, the order (sequence) of the nucleotides in the probe can provide information about the order in the target. Thus, an experiment showing that a DNA molecule with a known sequence of CCCC preferentially hybridizes to a sample DNA molecule can provide information about the identity and sequence of the target DNA — GGGG in this example. The difficulty comes in trying to distinguish the hybridization of a perfect match from a single-base mismatch – *e.g.*, a probe of sequence CCCT (instead of CCCC) in the prior example. Through careful control of hybridization conditions (*e.g.*, temperature, reagent concentrations, etc.), hybridization can be used to differentiate the strength of binding of a perfect match and a single-base mismatch to a particular target.

B. The Technology of the Asserted Patents

Having dropped one patent, Affymetrix now asserts five patents against Illumina in this case. While all relate generally to nucleic acid hybridization and (in most instances) array technology, each of the patents specifically implicates different aspects of these broad technology

[1] The nucleotide A can also pair with a uridine nucleotide (or "U"), but in nature U nucleotides are usually found in ribonucleic acid ("RNA") rather than DNA.

areas. The five patents can generally be broken down into three categories: (1) The Bead Patents (U.S. Patent Nos. 6,646,243, Ex. A ("the '243 patent") and 6,355,432, Ex. B ("the '432 patent")); (2) The Chip Patents (U.S. Patent Nos. 5,545,531, Ex. C ("the '531 patent") and 6,399,365, Ex. D ("the '365 patent")); and (3) The Software Patent (U.S. Patent No. 5,795,716, Ex. E ("the '716 patent"). The Bead Patents generally have claims relating to beads that have biological molecules attached to them. In many instances, the beads are so small that they look like dust to the naked eye. The Chip Patents generally relate to the basic components of DNA arrays or chips. The Software Patent generally relates to a computer program for manipulating intensity data from unknown sample DNA molecules hybridized to surface-bound probes to determine the sequence of the target nucleic acids. A more detailed overview of each patent-in-suit is provided below.

C. Illumina's BeadArray™ Technology

Illumina was formed in 1998 based on patented technology licensed from researchers at Tufts University. Illumina's technology uses bulk, inexpensive manufacturing steps that greatly reduce the cost of producing high-quality bead arrays. While Affymetrix's approach makes so-called "ordered" arrays, in that each step of its process grows known oligonucleotides at known locations on a substrate, Illumina uses a "random" approach to prepare arrays of beads to which oligonucleotides are bound. Illumina's "random" or "self-assembly" process involves the use of very small beads onto which oligonucleotides of different sequences are attached. Large numbers of these oligonucleotide-coated beads are made in batch chemical processes. Beads having oligonucleotides of different sequences bound to them (each referred to as a different "bead type") are then pooled together in larger bead pools.

To produce one of its random arrays, Illumina's bead pool is then poured over pits etched into the ends of fibers in a fiber-optic bundle or etched into a microchip. Because the pits are sized to accept one bead each, the beads then "self-assemble" randomly into the pits, much like marbles will fall into the pits of a Chinese checkerboard. Like the marbles on the checkerboard, there is no way to know in the case of Illumina's very small beads what bead type will assemble into what pit.

In order to determine which bead types are in which pits, Illumina, as part of its manufacturing process, includes nucleic-acid-based codes on its beads (sometimes incorporated with the probes) so that they can be later identified through a "decoding" process.

Illumina's BeadArray technology does not employ any ordered methods of building the different oligonucleotide sequences on a single surface (*i.e.*, *"in situ"* synthesis). In fact, it is virtually impossible using Illumina's technology to create identical arrangements of beads, while Affymetrix's patented technology is intended to and used to create identical copies of the same arrays. Moreover, when actually using these arrays for their intended scientific research purposes, Illumina employs special enzymatic-based assays to determine genetic information about a target nucleic acid, rather than the discrimination of single-base mismatches through hybridization experiments. Illumina's assays help enhance or sharpen the signals so that the sequence information can be more reliably obtained.

II. LEGAL PRINCIPLES

The legal principles governing claim construction were recently summarized and clarified by the *en banc* Federal Circuit in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-24 (Fed. Cir. 2005). The Court explained that claim terms "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* at 1312-13; *see also Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004). To determine this meaning, "the court starts the decision making process by reviewing the same resources as would that person, *viz.*, the patent specification and the prosecution history." *Phillips,* 415 F.3d at 1313; *see also Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005) ("We cannot look at the ordinary meaning of the term . . . in a vacuum . . . we must look at the ordinary meaning in the context of the written description and the prosecution history."). Thus, claim construction rests primarily on three sources of intrinsic evidence — the claims, the specification, and the prosecution history.

In many cases, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Phillips,* 415 F.3d at 1314. For example, claim terms must be interpreted in a way that gives meaning to each word. *Id.* (explaining that "steel baffles" must have a different meaning than "baffles"); *Texas Instruments Inc. v. U.S. I.T.C.,* 988 F.2d 1165, 1171 (Fed. Cir. 1993) (rejecting a construction that would "render the disputed claim language mere surplusage" and therefore "read an express limitation out of the claims"). It is also necessary that the interpretation of any one element be consistent with other terms in the same claim. *See Phillips,* 415 F.3d at 1314; *Hockerson-Halberstadt, Inc. v. Converse, Inc.,* 183 F.3d 1369, 1374 (Fed. Cir. 1999) ("Proper claim construction, however, demands interpretation of the entire claim in context, not a single element in isolation.").

The claims "do not stand alone," however, and "must be read in view of the specification, of which they are part." *Phillips*, 415 F.3d at 1315. The specification will often provide "the single best guide to the meaning of a disputed term." *Id.* One reason for this is that "[t]he claims are directed to the invention that is described in the specification; they do not have meaning removed from the context from which they arose." *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001); *see also Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1347 (Fed. Cir. 2004) ("Although it is improper to read a limitation from the specification into the claims, '[c]laims must be read in view of the specification, of which they are a part.'").

Finally, the intrinsic evidence includes the prosecution history, which "like the specification . . . provides evidence of how the PTO and the inventor understood the patent . . . [and] was created by the patentee in attempting to explain and obtain the patent." *Phillips*, 415 F.3d at 1317. In particular, "[t]he prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution." *Rheox, Inc. v. Entact, Inc.,* 276 F.3d 1319, 1325 (Fed. Cir. 2002) (citing *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995)); *see also Elkay Mfg. v. Ebco Mfg. Co.,* 192 F.3d 973, 979 (Fed. Cir. 1999) ("Arguments made during the prosecution of a patent application are given the

same weight as claim amendments."). This "makes sense, because '[t]he public has a right to rely on such definitive statements made during prosecution.'" *Spectrum Int'l Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1378 (Fed. Cir. 1998). The law thus dictates that "[c]laims may not be construed one way in order to obtain their allowance and in a different way against accused infringers." *Id.* at 1379 (citing *Southwall*, 54 F.3d at 1576).

III. THE BEAD PATENTS

A. The '243 Patent

The '243 patent relates generally to a method and an apparatus for analyzing nucleic acid binding using a substrate having an area less than 1 cm^2 with at least 1000 beads with nucleic acids attached thereto, binding fluorescently-labeled target nucleic acids to the nucleic acids on the beads, and then detecting the fluorescent labels and storing the information. In discussing the method and apparatus, the '243 patent discusses the preparation and use of a substrate upon whose surface a plurality of polymer sequences are synthesized. More specifically, the '243 patent discusses application of photolithographic techniques derived from the semiconductor industry to synthesize polymers on a substrate in a process involving sequential steps of adding one monomer per synthesis cycle.

Claim 14 is one of the independent claims asserted by Affymetrix:

> 14. An apparatus for analyzing nucleic acid binding, comprising:
>
> a ***substrate*** that comprises at least 1000 different spheres, beads, or particles having different species of nucleic acids attached thereto, the area of the substrate containing the at least 1000 spheres, beads or particles being less than 1 cm^2, at least some of the nucleic acids being bound to fluorescently labeled ***target nucleic acids***;
>
> a laser energy source to illuminate the fluorescent labels;
>
> a detector to detect a fluorescent label bound to said target nucleic acids; and
>
> a data collection system for storing fluoresced light intensity.

'243 col. 30:53-67 (emphasis added to highlight the disputed terms). The asserted dependent claims relate to, *inter alia*, greater numbers of beads and the manner of detecting fluorescence.

1. "substrate"

Illumina's Construction	Affymetrix's Construction
a material having a rigid or semi-rigid surface on which polymers are synthesized	a material having a rigid or semi-rigid surface

The intrinsic evidence uniformly establishes that a substrate for purposes of the '243 patent is not just a rigid or semi-rigid material with a surface, but rather is one whose surface is a support for polymer synthesis. Affymetrix specifically defined the term "substrate" as recited in Illumina's proposed construction, and it repeatedly described the alleged invention of the '243 patent as a method and apparatus for the synthesis of polymers on a substrate surface. The scope of the claims of the '243 patent must be construed accordingly. *See, e.g., Netword,* 242 F.3d at 1352-53 (affirming construction limiting claim term to the specific disclosures and remarks describing claimed invention in the specification). Affymetrix's proposed construction should be rejected because it is incomplete as established by the intrinsic evidence.

The '243 specification. The '243 patent defines "substrate" and consistently uses the term in describing the '243 invention as a material on whose surface polymers are synthesized. The '243 patent includes a Glossary that defines "substrate" as proposed by Illumina:

> ***A material having a rigid or semi-rigid surface.*** In many embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it may be desirable to physically separate ***synthesis regions for different polymers*** with, for example, wells, raised regions, etched trenches, or the like. According to other embodiments, ***small beads may be provided on the surface which may be released upon completion of the synthesis.***

'243 col. 7:35-43 (emphasis added). This definition is clear that synthesis is performed on the "substrate" regardless of the embodiment — whether a flat substrate, a substrate with etched or raised regions, or a substrate of beads provided on a surface that are released after synthesis. This

definition always refers to the substrate and its surface in the context of "synthesis" or "synthesis regions."[2]

It is important to note that the third sentence quoted above ('243 col. 7:40-43) provides the ***only*** mention in the entire specification of the use of beads as a support for different polymers, as required by the asserted claims of the '243 patent.[3] Similarly, there is only one passage in the entire '243 specification that Affymetrix has argued supports the claim limitation requiring a density of 10^3 nucleic acid sequences in less than 1 cm^2 — this description is in the "Polymer Synthesis" section of the specification and clearly ties these density limitations to regions of synthesis.[4] '243 col. 15:8-15 ("In some embodiments ***a single substrate supports more than about 10 different monomer sequences*** and preferably more than about 100 different monomer sequences . . . . Of course, ***within a region of the substrate in which a monomer sequence is synthesized***, it is preferred that the monomer sequence be substantially pure." (Emphasis added)). If there is any written description support for the claims at all, they must be construed to require the substrate to be the place where synthesis occurs.

Beyond the Glossary, the specification of the '243 patent uniformly refers to the alleged invention as involving a substrate where polymer sequences are synthesized on the surface of the substrate. For example, the '243 patent begins with the Abstract, which specifies that the "substrate" is the material on which polymer synthesis is performed:

> A method and apparatus for ***preparation of a substrate containing a plurality of sequences***. Photoremovable groups are attached to a surface

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[2] The definition of "substrate" in the '243 patent is entirely consistent with the ordinary meaning of "substrate" in the dictionary: "[ELECTR] The physical material on which a microcircuit is fabricated; used primarily for mechanical support and insulating purposes, as with ceramic, plastic, and glass substrates; however, semiconductor and ferrite substrates may also provide useful electrical functions." Ex. F at 2061 (*McGraw-Hill Dict. of Sci. & Tech. Terms* (6th ed. 2002)).

[3] *See* Ex. G (App. No. 10/098,203 – 1/28/03 Response at 4) ("[P]age 14, line 13 ['243 col. 7:41] states that 'beads' can be substrates."). Indeed, Affymetrix pointed the Patent Office to this exact language in combination with a general oligonucleotide probe density disclosure to argue that a bead substrate is a polymer synthesis region. *See* Ex. H (App. No. 10/125,530 – 8/19/04 A't at 10) ("It is evident that ***each bead*** will contain a unique nucleic acid species (oligonucleotide) and therefore ***consist of a synthesis region as one nucleic acid species would be synthesized per bead***.").

[4] *See* Ex. G (App. No. 10/098,203 – 1/28/03 Response at 4) ("'1,000' (shown as '10^3') sequences on a support is shown on page 29, line 22 ['243 col. 15:11]").

> of a substrate. Selected regions of the substrate are exposed to light so as to activate the selected areas. A monomer, also containing a photoremovable group, is provided to the substrate to bind at the selected areas. ***The process is repeated using a variety of monomers such as amino acids until sequences of a desired length are obtained.***

'243 patent, Abstract (emphases added); *see, e.g.*, *Tate Access Floors, Inc. v. Maxcess Tech., Inc.*, 222 F.3d 958, 965 n.2 (Fed. Cir. 2000) (using the patent abstract to ascertain claim term meaning).

The Summary of the Invention similarly describes the alleged invention of the '243 patent as providing an improved method and apparatus for the preparation of a variety of polymers on a substrate surface using photolithography. *See, e.g.*, *Poly-America, L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) (citing the Summary of the Invention to define a limitation in the claims). The Summary first describes the invention as "[a]n improved method and apparatus ***for the preparation of*** a variety of polymers." '243 col. 2:66-67 (emphasis added). The Summary then refers to the "substrate" as a material on whose surface polymers are synthesized:

> By using the lithographic techniques disclosed herein, it is possible to direct light to relatively small and precisely known locations on the substrate. It is, therefore, possible to ***synthesize polymers of a known chemical sequence at known locations on the substrate.***
>
> ***The <u>resulting</u> substrate will have a variety of uses*** including, for example, screening large numbers of polymers for biological activity.

'243 col. 3:25-32 (emphasis added); *see also* '243 col. 3:62-65 ("By selectively deprotecting regions on the substrate and flowing predetermined monomers through the reactor space, ***desired polymers at known locations may be synthesized.***").

The '243 specification further contains a "Polymer Synthesis" section that details how polymers are proposed to be synthesized on a substrate. *See* '243 cols. 10:51-15:24; *see also* '243 col. 21:2-5. Again, the descriptions use "substrate" to mean a support for polymer synthesis rather than simply a material with a rigid or semi-rigid surface:

> For example, the substrate may contain raised or depressed regions on which the synthesis takes place. ***The substrate and its surface preferably form a rigid support on which to carry out the reactions described herein.***

'243 col. 10:62-66 (emphasis added) & Fig. 1. Without exception, every embodiment described in this section is related to the use of substrates for polymer synthesis. *See, e.g.*, '243 col. 11:25-33; cols. 11:34-12:3; cols. 13:59-14:8; col. 14:24-67 & figs. 1-7; col. 15:1-19. The "General Section" of the specification similarly requires synthesis on the "substrate." *See* '243 cols. 8:30-46 (discussing use of linker molecules on the surface of the substrate either to aid in polymer synthesis or receptor recognition); 8:54-61 & 23:39-47 (explaining the direct relationship between light-exposed regions and polymer synthesis areas on the substrate surface); 8:62-10:2 (describing the conceptual process for sequential synthesis of polymers on a substrate surface).

This is not a case where only some embodiments call for synthesis of polymers on a substrate. To the contrary, the specification concludes by specifically referring to the ***inventions*** of the '243 patent as requiring synthesis on the substrate: "The present inventions provide greatly improved methods and apparatus for ***synthesis of polymers on substrates***." '243 col. 29:30-31 (emphasis added). The '243 patent specification in its entirety dictates that the term "substrate" must be construed to be the place where synthesis occurs. *SciMed Life Sys., Inc. v. ACS, Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) (limiting construction of a claim term based on the description of the invention throughout the specification).

The '243 prosecution history. During prosecution of the applications in the '243 patent family, Affymetrix confirmed what it repeatedly stated in the specification of the '243 patent — that the alleged invention was making and using a substrate upon whose surface polymers have been synthesized. For example, during prosecution of the parent application to which the '243 patent claims priority, Affymetrix expressed the same interpretation of the term "substrate" when it told the Patent Office that the invention "relates to a method and device for ***forming*** diverse chemical sequences such as amino acid sequences on a solid substrate. ***The substrate is then used*** in, for example, ligand/antiligand studies." Ex. I (App. No. 07/492,462 – 5/18/90 Petition at 1). Affymetrix used the term "substrate" during prosecution to refer to a material with a surface upon which polymers have been synthesized.

In that same application, Affymetrix distinguished a Lowe prior art reference by arguing that this reference did not disclose how to synthesize sequences at known locations on a substrate, but instead taught how to attach pre-synthesized sequences:

> ***An important goal of the invention claimed herein is the synthesis of diverse chemical sequences at known locations on a substrate***, followed by the screening of these diverse sequences for interactions with, for example, an antibody or other receptor. ***Lowe et al. do not provide even a clue as to how this goal would be achieved.*** Lowe et al. propose to attach a number of materials which have already been synthesized to a substrate. . . . ***Lowe et al. do not show or suggest synthesis of diverse compounds.*** This problem of synthesizing large scale chemical diversity has plagued the art for many years and was not solved by Lowe et al. . . . Although not entirely clear, Lowe et al. then propose to use these immobilized, pre-synthesized materials to test for the presence of a compound which is known to interact with the material (see, e.g., the specification and Claim 16), and ***did not propose the in situ synthesis of the ligand.***

Ex. J (App. No. 07/492,462 – 3/26/97 A't at 13-14) (emphases added).

Competitors are entitled to rely upon Affymetrix's repeated characterizations of the "substrate" of the alleged invention of the '243 patent as a material upon which polymers are synthesized. *See, e.g.*, *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000). Having made such representations regarding the scope of its alleged invention, Affymetrix cannot take them back now simply because they are inconsistent with its current litigation goals. *See id.* (noting that representations made in prosecution history are not a "mulligan" that can be taken back).

2. "target nucleic acids"

Illumina's Construction	Affymetrix's Construction
sample nucleic acids with sequence to be determined	nucleic acids that have an affinity for the nucleic acid attached to the bead

The dispute before the Court is whether the term "target nucleic acids" should be defined backwards as anything that binds to the nucleic acid attached to a bead (as proposed by Affymetrix) or if the term should be given its plain meaning.

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; *see also* Ex. F at 2105 (*McGraw-Hill Dictionary of Scientific and Technical Terms* (6th ed. 2002)) (defining "target compound" as "the molecule of interest" in chemical synthesis). Illumina's proposed construction reflects the meaning of "target" in the intrinsic record. Conversely, Affymetrix's construction seeks an overbroad interpretation devoid of any substance as to what a "target nucleic acid" really is.

The '243 specification. The specific term "target nucleic acids" does not appear anywhere in the '243 patent other than in the claims. All available evidence, however, confirms that this term would be understood by one of ordinary skill in the art to mean nucleic acids from a sample about which information is sought.

The plain language of the claims, ***themselves***, compels Illumina's proposed construction. Asserted independent claim 14 establishes that "target nucleic acids" are nucleic acids from a sample about which information is desired:

> ***An apparatus for analyzing nucleic acid binding***, comprising:
> a substrate that comprises at least 1000 different spheres, beads or particles having different species of nucleic acids attached thereto, . . . at least some of the nucleic acids being bound to fluorescently labeled ***target nucleic acids*** . . .

'243 claim 14 (emphasis added). The plain language of claim 14 requires that the target nucleic acids are those being analyzed for information or characterization.[5]

The entire specification of the '243 patent relates to the analysis of biological polymers of interest such as nucleic acids. The '243 patent states that the alleged invention allows investigation of "receptors." '243 col. 6:45-46. The specification further describes how nucleic acid binding can

[5] Similarly, asserted claim 35 establishes that "target nucleic acids" are nucleic acids from a sample from which biological activity information is to be gained.

be used to determine all or part of a sequence complementary to "receptors" such as target nucleic acids:[6]

> The polymers prepared on a substrate according to the above methods will have a variety of uses including, for example, ***screening for biological activity. In such screening activities, the substrate containing the sequences is exposed to an unlabeled or labeled receptor*** . . . .
>
> ***The receptor molecules may bind with one or more polymers on the substrate.*** The presence of the labeled receptor and, therefore, the presence of a sequence which binds with the receptor is detected . . . . ***The sequence of the polymer at the locations where the receptor binding is detected may be used to determine all or part of a sequence which is complementary to the receptor.***

'243 col. 10:3-24 (emphasis added); *see also* '243 col. 17:64-18:3 ("The entire derivatized substrate is then exposed to a ***receptor of interest***, preferably labeled with, for example, a fluorescent marker . . . . The receptor will preferentially bind to certain regions of the substrate which contain complementary sequences."). The specification describes how to determine all or part of a sequence of a nucleic acid of interest through analyzing its binding to polymers with complementary sequences on the substrate.

The '243 prosecution history. The prosecution history of a parent application to which the '243 patent claims priority confirms Illumina's interpretation that "target nucleic acids" are the samples to be analyzed for sequence information. *See, e.g.*, *Biovail Corp. Int'l v. Andrx Pharms, Inc.*, 239 F.3d 1297, 1301-02 (Fed. Cir. 2001) (applying arguments limiting claim scope made in the prosecution history of a parent application to a continuation). Specifically, Affymetrix amended a pending claim and explained that "the ***target molecules analyzed by the array are the receptors*** (***e.g., nucleic acids*** or proteins) in conformity with the teaching of the specification that nucleic acid arrays are also useful for analyzing a variety of receptors (see, e.g., paragraph bridging pp. 15-16)." Ex. M (App. No. 08/456,598 – 5/15/00 A't at 2). The specification section referred to in Affymetrix's remarks explains that the prepared substrate (with nucleic acids synthesized on it)

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[6] The specification includes nucleic acids as an example of "receptors" that can be used in the invention. '243 col. 6:28-40.

can be used to determine information about various sample targets, including "nucleic-acid sequences which bind to proteins, finding sequence-specific binding drugs, identifying epitopes recognized by antibodies, and evaluation of a variety of drugs for clinical and diagnostic applications . . . ." '243 col. 8:18-29.

Illumina's proposed construction explains the meaning of "target nucleic acids" as claimed and described for investigation of receptors, such as target ***nucleic*** acids, about which information may be determined by exposing them to and then analyzing their binding to known nucleic acid sequences synthesized on the surface of the claimed substrate. *See, e.g.*, *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 450 (Fed. Cir. 1986) (construing asserted claim in light of inventor's purpose as disclosed in specification). Affymetrix's proposed construction does not and should be rejected.

B. The '432 Patent

The '432 patent generally relates to the use of a plurality of "beads being coded with an encoding system" where a target specific sequence (probe) is attached to the beads. The '432 patent discusses the use of Very Large Scale Immobilized Polymer Synthesis ("VLSIPS™") to make substrates with attached binding polymers of known recognition specificity to a target polymer to be analyzed for information. As further discussed in the '432 patent, the VLSIPS™ substrate can be used for sequencing, fingerprinting, or mapping of target polymers such as nucleic acids or polypeptides. Claim 1 of the '432 patent, from which all of the other claims in the patent depend, reads as follows:

> 1. A collection of beads comprising a plurality of beads which have binding polymers of different ***target specific sequence*** attached thereto; ***said beads being coded with an encoding system*** whereby the target specific sequence of the polymer attached to the bead can be identified.

'432 col. 82:51-55 (emphasis added to highlight the disputed terms). The dependent claims then limit the claims to oligonucleotides of certain lengths and minimum numbers.

1. "said beads being encoded with an encoding system"

Illumina's Construction	Affymetrix's Construction
said beads having a property associated with each bead (separate from the binding polymer) that can be used to distinguish one bead from another	said beads being distinguishable one bead from another

The parties appear to agree that one bead must be distinguishable from another, but Affymetrix's proposed construction is silent on how the beads are "coded with an encoding system" to allow this. The dispute before this Court is whether the intrinsic record, including the claim language and specific representations Affymetrix made to the Patent Office that an "encoding system" is a different entity than the binding polymer, requires adoption of Illumina's proposed construction.

Illumina's proposed construction reflects the claim language distinction between the binding polymers attached to the bead substrate and the encoding system coding the bead. Independent claim 1 of the '432 patent is explicit that the "binding polymers" and the "encoding system" are separate things. The claim specifies "a plurality of ***beads which have binding polymers of different target specific sequence attached thereto***; said ***beads being coded with an encoding system*** . . . ." '432 claim 1 (emphasis added). The plain language of the claim requires that the binding polymers are attached to beads, which ***have been coded*** with an "encoding system." The language of the claim excludes the circumstance where the binding polymers are the encoding system. Indeed, this is exactly what Affymetrix told the Patent Office during prosecution.

The '432 prosecution history. During prosecution of the parent application to the '432 patent at issue here, Affymetrix provided express guidance on the meaning of the term "encoding system" in a series of amendments to gain claim allowance. Like the asserted claims here, the then-pending claims initially required a collection of substrates, "wherein different substrates bear different reagents and an encoding system." *See, e.g.*, Ex. N (App. No. 09/362,089 ("'089 App.") – 5/2/00 A't at 1 (claim 58)). In response to an examiner rejection stating that it was unclear whether

each substrate bore an encoding system, Affymetrix amended the claims, adding the limitation "an individual bound substrate thereby bears a tag of an encoding system" in order to:

> [M]ake clear that (1) ***the reagent and tag are different entities***, (2) ***an individual bound substrate bears a tag of an encoding system***, and (3) the tag of the encoding system is on the bound substrate at least after binding.

Ex. O ('089 App. – 2/28/01 A't at 9 (emphasis added)). Thus, in this amendment, Affymetrix clarified that the "encoding system" carried by each substrate such as a bead is a ***different*** entity than the reagent (*i.e.*, the "binding polymer" of the '432 patent claims).[7] *See, e.g.*, *Biovail Corp. Int'l*, 239 F.3d at 1301-02.

Following a second amendment and rejection, Affymetrix met with the examiner to discuss "[c]hanges to the claims ***to clarify [the] distinction between the encoding system and the reagent as a binding reagent***." Ex. P ('089 App. – 9/20/01 Interview Summary). Claims were allowed following amendments agreed upon during the Examiner Interview, clarifying the distinction between the encoding system and the binding reagent, as exemplified by the relevant limitation in pending claim 39:

> [A] collection of substrates, wherein different ***substrates bear different binding reagents and a binding reagent encoding system***, whereby the target molecule binds to one or more of the substrates via the reagent.

Ex. Q ('089 App. – 9/25/01 A't at 4-5 (emphasis added)). This demonstrates that the "encoding system" carried by each substrate such as a bead is a separate, distinct entity from than the binding reagent.

Affymetrix made these statements and related claim amendments to gain claim allowance. As such, they constitute intentional representations to the public concerning the scope and meaning of the term "encoding system" on which competitors are entitled to rely. *See, e.g.*, *Hockerson-*

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[7] U.S. Application No. 09/362,089 shares the same specification as its continuation, the '432 patent. The '432 patent specification identifies reagents as binding polymers in that the reagents are "capable of interacting with their specific targets while attached to the substrate." '432 col. 6:33-35; *see also id.* col. 6:28-30 ("The present invention relies in part on the ability to synthesize or ***attach specific recognition reagents*** at known locations ***on a substrate*** . . . .").

Halberstadt, 222 F.3d at 957 (representations made in the prosecution history are not a "mulligan" that can be taken back).

The '432 specification. In the above prosecution history, Affymetrix referred the Patent Office to certain portions of the specification allegedly teaching "various encoding systems suitable for use in the claimed invention." Ex. O ('089 App. – 2/28/01 A't at 7). In particular, Affymetrix identified a "description of the encoding system" in the '432 specification at col. 21:40-67:[8]

> In the extreme case, ***each probe might be attached to a single bead*** or substrate and the beads sorted by whether there is a binding interaction. Those ***beads which do bind might be encoded*** to indicate the subsequence specificity of reagents attached thereto.
>
> . . . . After the relatively small number of beads which have bound the target have been collected, the encoding scheme may be read off to determine the specificity of the reagent on the bead. ***An encoding system may include a magnetic system, a shape encoding system, a color encoding system, or a combination of any of these***, or any other encoding system.

'432 col. 21:47-64 (emphasis added). Each of the described encoding systems specifically contemplated by Affymetrix — magnetic, shape, color, or combination — is a bead property or characteristic distinct from the probe (binding polymer) attached to the bead.[9] Thus, the specification confirms Illumina's proposed construction – regardless of the type of encoding system used, it must be something separate from and a different entity than the binding polymer.

2. "target specific sequence"

Illumina's Construction	Affymetrix's Construction
a known sequence of a polymer that binds with specificity to the target at the sequence to be determined	a known polymer sequence that has affinity for another sequence

[8] Affymetrix's prosecution history statement cited to a substitute specification that was also filed as Paper No. 6 in the '432 patent prosecution history. *See* Ex. R (App. No. 09/585,659 – 6/15/00 A't at 1 & Enclosure). For the Court's convenience, the substitute specification citations are translated to the corresponding '432 specification cites.

[9] The other section Affymetrix identified as providing a "description of 'coding' applications and the use of nucleotide sequences for encoding" is limited to examples involving use of a molecule, such as a nucleic acid, as an information-containing marker to provide information such as manufacturer, date, source, or origin of genetic material for products, drugs, food, animals, etc. None of these uses involve a binding polymer. *See* '432 cols. 58:8-60:19.

The parties appear to agree that a "target specific sequence" is a known sequence of a polymer. The dispute appears to be whether the "target specific sequence" is specific to a sequence in the "target" (as proposed by Illumina) or whether it is merely something that can bind to something else (as proposed by Affymetrix). The intrinsic record compels Illumina's proposed construction, making it clear that target sequence specific recognition reagents are used to sequence, fingerprint, and map biological polymers. Consequently, Illumina's proposed construction should be adopted and Affymetrix's proposed construction should be rejected as overbroad.

The '432 patent does not claim just any binding polymer of any sequence, but rather "binding polymers of ***different target*** specific sequence attached thereto." The asserted claims require, therefore, that each "target specific sequence" constitutes a unique molecule whose sequence is already known and that can bind to a particular target.

The '432 specification confirms that a "target specific sequence" is a sequence specific recognition reagent that can be used for sequencing, fingerprinting and mapping biological macromolecules. *See, e.g.*, '432 Abstract; *see also* '432 col. 1:27-29. Because "it has become very important to determine the genetic sequences of nucleotides which encode the enzymes, structural proteins, and other effectors of biological functions" as well as those nucleotide sequences involved in control and regulation of gene expression, the '432 invention provides a "less expensive, highly reliable, and labor efficient means for sequencing biological macromolecules."[10] '432 cols. 1:33-2:26. Thus, the '432 specification confirms that "target specific sequence" reagents are used to determine information about the target for which the reagent is specific. *See, e.g.*, *Tate Access Floors,* 222 F.3d at 965 n.2 (using the patent abstract to ascertain claim term meaning).

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[10] Sequence determination, as defined in the '432 specification, includes both "complete sequence determination, to the level of the sequence of individual subunits along the entire length of the target sequence," as well as "sequence homology," but in either case, "the sequence is determinable at selective resolution or at particular locations" useful for fingerprinting or mapping of particular target sequences. '432 col. 7:11-23.

The Summary of the Invention further confirms that a "target specific sequence" is a reagent whose sequence is both known and specific to the target polymer about which information is sought. *See, e.g.*, *Poly-America*, 383 F.3d at 1310 (citing the Summary of the Invention to define a limitation in the claims). For example, the Summary of the Invention states:

> The invention is enabled by the development of technology to prepare substrate on which specific reagents may be either positionally attached or synthesized. . . . These ***reagents specifically recognize subsequences in a target polymer and bind thereto***, producing a map of positionally defined regions of interaction . . . convertible into actual features recognized, and thus would be present in the ***target molecule of interest***.
>
> As indicated, the ***sequence specific recognition reagents will often be oligonucleotides which hybridize with fidelity and discrimination to the target sequence***. For use with other polymers, monoclonal or polyclonal antibodies having high sequence specificity will often be used.

'432 col. 7:25-41 (emphasis added); *see also* '432 col. 12:28-46. The specification also explains that the specific sequence recognition reagents include both: (1) "***oligonucleotide probes which hybridize with specificity to subsequences found on the target sequence***" for sequencing target polynucleotides, and (2) antibodies specific for particular polymer subsequences useful for sequencing of non-polynucleotides such as a polypeptide. '432 cols. 6:54-61 (emphasis added), 2:41-50, 16:1-8, 8:18-30.

The intrinsic evidence confirms, therefore, that the "target specific sequence" is a reagent whose sequence is known and specific to a particular "target" about which information is sought.

IV. THE CHIP PATENTS

A. The '531 Patent

The '531 patent generally relates to a biological chip plate with multiple arrays of probes on a single surface. The '531 patent states that the VLSIPS™ process of light-directed probe synthesis allows the production of biological chips with hundreds of thousands or more different molecular probes. The '531 patent further discusses that for VLSIPS™, the probes can be "any molecules whose synthesis involves sequential addition of units" ('531 col. 10:16-17), and the resulting synthesized probes are arrayed on the surface of a chip in addressable rows and columns.

The '531 patent has four claims, claims 1 and 3 of which are independent. Independent claim 1 reads:

> 1. A method for making a biological chip plate comprising the steps of:
> (a) providing a body comprising a plurality of wells defining spaces;
> (b) providing a wafer comprising on its surface a plurality of ***probe arrays***, each probe array comprising a collection of probes, at least two of which are different, ***arranged in a spacially defined and physically addressable manner***;
> (c) attaching the wafer to the body so that the ***probe arrays*** are exposed to the spaces of the wells.

'531 col. 12:40-51 (emphasis added to highlight the disputed terms).[11] Dependent claims 2 and 4 restrict the probes of claims 1 and 3 (respectively) to be DNA or RNA.

1. "probe array"

Illumina's Construction	Affymetrix's Construction
a collection of probes, at least two of which are different, that are surface-immobilized (chemically-linked) to a single surface	a collection of surface-immobilized molecules, at least two of which are different, that can be recognized by a particular target

Illumina's proposed construction combines the glossary definitions of "probe" and "array" set forth in the '531 patent and clarifies that the probes constituting a probe array must be chemically linked to the same single surface. Affymetrix's proposed construction ignores the intrinsic evidence, including its own admissions during prosecution, and seeks to broaden the claims well beyond what is described in the patent.

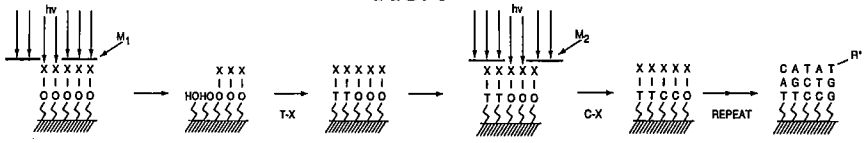
The '531 claims require that the probes in the array are on the single surface of one wafer. Asserted claims 1-4 all require "***a wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different.***" '531 claims 1-4 (emphasis added). The plain language of the claims confirms Illumina's construction that each probe in each array, and indeed each array, are on the same surface of a wafer to create the biological chip plate for concurrent processing of multiple biological chip assays.

[11] Independent claim 3 contains the same two claim limitations to be construed as noted in claim 1.

The '531 specification. The '531 specification further confirms Illumina's proposed construction that the probes in an array are immobilized on a single surface. While both parties agree that the '531 specification explicitly defines a probe as "a surface-immobilized molecule" ('531 patent, col. 3:39-40), Affymetrix ignores the definition of "array" and its requirement that it constitute "a collection of probes . . . arranged in a spacially defined and physically addressable manner." *Id.* at col. 4:1-3. The full term "probe array" must be considered in light of the intrinsic evidence, which requires that two or more probes must be chemically linked to a single surface.

The '531 specification provides a detailed description of how to "immobilize" the probes in an array to a single surface through direct synthesis of the probes onto the substrate using either VLSIPS™ or other *in situ* synthetic techniques.[12] '531 col. 9:11-10:17 (describing photolithographic synthesis of probe sequences on a substrate surface). Either method of synthesis requires chemical linkage of the probes to the same surface of a substrate, as shown in Figure 8:

FIG. 8



'531 fig. 8 (modified); *see also* '531 cols. 9:28-64, 10:10-17. All embodiments discussed in the specification refer to "immobilization" in the context of chemical linking of the polymer to a surface. There is no description of any other "immobilization."

The '531 specification further teaches that every probe in a probe array is immobilized on ***a single surface***, as shown in every described embodiment of the '531 invention. One embodiment

[12] U.S. Patent 5,143,854, PCT WO 92/10092, PCT WO 90/15070, U.S. App. Nos. 08/249,188, 07/624,120, and 08/082,937 all incorporated by reference describe the technique of immobilizing polymers such as oligonucleotides on a substrate surface by chemically synthesizing the polymer directly on the substrate. Likewise, the alternative embodiment of U.S. Patent No. 5,384,261 requires that the probes are directly synthesized on a substrate using a chemical process. *See* Ex. S.

includes multiple probe arrays synthesized on the surface of a wafer.[13] *See, e.g.*, '531 cols. 8:1-5, 8:28-31; figs. 4, 5 ("FIG. 5 depicts a cross-section of this embodiment, showing the wafer 510 having a substrate 520 . . . and ***a surface 530 to which is attached an array of probes 540.***" (Emphasis added.)). For this embodiment, it is clear that all probes in an array and, indeed, all arrays on the wafer, must be on a single surface. Another embodiment, one that is not implicated by the claims, uses individual biological chips, each attached to the bottom of a preformed well, in which a single chip surface contains one probe array. *See, e.g.*, '531 cols. 7:57-67, 8:22-26; figs. 3, 6, 7 ("Individual biological chips 630 are attached to the bottom of the wells so that ***the surface containing the array of probes*** **640** is exposed to the well space where the sample is to be placed." (Emphasis added));

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FIG. 5

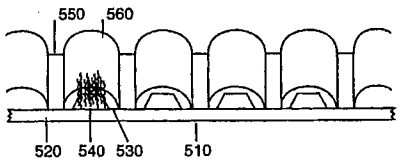
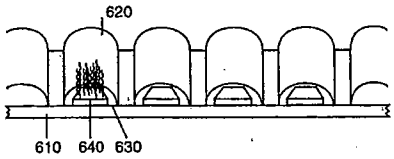


FIG. 6



Figures 5 and 6 of the '531 patent, reproduced above, demonstrate that regardless of the particular embodiment, the '531 specification consistently shows that all of the probes in any probe array (540 for embodiment #1, 640 for embodiment #2) are chemically linked to a single surface (530, 640);

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The '531 prosecution history. The prosecution history confirms that the probes in a probe array are all immobilized on a single surface. For example, in response to a PTO rejection based on U.S. Patent No. 5,143,854 to Pirrung *et al.*, Affymetrix gave the examiner permission to conform the claims to require the probe arrays to be on the surface of a wafer. *See* Ex. U (App. No.

[13] The '531 specification defines a wafer as a substrate with "***a surface to which one or more arrays of probes is attached.***" '531 col. 4:4-5.

08/476,850 – 3/6/96 Office Action at 3); Ex. V (App. No. 08/476,850 – 3/18/96 Interview Summary); Ex. W (App. No. 08/476,850 – 3/20/96 Interview Summary). As a predicate to allowance, the examiner amendment replaced the language describing a wafer "having a plurality of probe arrays" in original claim 67 with a wafer "comprising ***on its surface*** a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different . . . ."[14] *Compare* Ex. X (App. No. 08/476,850 Original Claim 67 at 30) *with* Ex. Y (App. No. 08/476,850 – 3/25/96 Notice of Allowability). The claims must be construed as proposed by Illumina to require at least the probes of each probe array (if not all probe arrays) to be on a single surface.

2. "arranged in a spacially defined and physically addressable manner"

Illumina's Construction	Affymetrix's Construction
each probe in an array is placed in a different pre-determined location on the surface	located in a particular location and capable of being accessed

The dispute before the Court is whether the probes in an array must be "arranged," *i.e.*, "placed" in pre-defined positions on the surface of the wafer or if each probe only has to be found somewhere on the wafer surface. Illumina's proposed construction reflects the claim language and the '531 specification's consistent descriptions that each probe is selected and assigned a specific location in an array depending on contemplated use. Indeed, this claim language was specifically added by the Examiner to clarify that the probes in a probe array must be "arranged" in an orderly fashion. Affymetrix's proposed construction conflicts with this intrinsic evidence.

The claims of the '531 patent explicitly require that each probe in an array be "arranged" in a particular way. The term "arranged" is not a term of art and is not specifically defined in the Definitions section of the '531 patent. It has a plain meaning in the claims, requiring specific placement or ordering, consistent with the dictionary definition of "arrange": "to put in correct,

[14] As amended, original claim 67 issued as '531 independent claim 3. Original claim 65, which issued as '531 independent claim 1, already contained the requirement that the probe arrays had to be on the surface of the wafer. *Compare* Ex. X (App. No. 08/476,850 Original Claim 65 at 30) *with* Ex. Y (3/25/96 Notice of Allowability at 2).

convenient, or desired order: adjust properly: dispose, place." Ex. Z at 120 (*Webster's Third New Int'l Dict.* (1993)). Only Illumina's proposed construction reflects the proper meaning of the term "arranged."

The '531 specification. The specification repeatedly and uniformly discusses the synthesis of probe arrays designed with probes placed in different pre-determined locations on a surface. The specification explicitly describes selecting probe content and arrangement of these probes in the array depending on the particular application desired. For example, in the background of the '531 invention, Affymetrix describes the advantage of using VLSIPS™ for producing biological chips or arrays having "probes arranged in arrays, ***each probe assigned a specific location***." '531 col. 1:15-16 (emphasis added). The specification also states that "the amount of information that can be stored on each plate of chips depends on the lithographic density which is used to synthesize the wafer." '531 col. 10:36-44. The specification further explains that "[t]he selection of probes and ***their organization in any array*** depends upon the use to which the biological chip will be put." '531 col. 10:45-47 (emphasis added). This organization means that specific probes or types of probes are "arranged" in certain pre-determined locations depending on the particular application contemplated. *See, e.g.*, '531 cols. 2:64-67; 8:61-9:1; 11:58-64.

B. The '365 Patent

The '365 patent generally relates to an array of biological polymers (*e.g.*, nucleic acids), with a housing surrounding the array to allow for chemical reactions to take place, and a bar code. The patent has several independent claims, many of which Affymetrix originally asserted but no longer accuses Illumina of infringing. One of the independent claims originally asserted by Affymetrix was claim 1 (upon which many of the remaining asserted dependent claims depend), which reads as follows:

> 1. A package for hybridization, comprising:
>
> a substrate comprising a first surface including a probe array with different probes comprising ***biological polymers immobilized on said first surface***; said probe array including a density exceeding 100 different biological polymers per cm^2; and

> a ***housing*** including a fluid cavity constructed and arranged for hybridization of a target to a probe of said probe array, said housing including a bar code.

'365 patent, col. 23:10-18 (emphasis added to highlight the disputed terms). All of the claims have some form of the limitation requiring "biological polymers immobilized on said first surface," although not all of the claims contain the limitation of a "housing" as set forth in claim 1.

1. "housing"

Illumina's Construction	Affymetrix's Construction
casing that separates the probe array from the atmosphere	a structure in which something is contained

The term "housing" in the '365 patent should be construed to be a casing that separates the probe array from the surrounding atmosphere. The word "housing" does not appear a single time in the specification of the '365 patent, just as it appeared nowhere in the patent application to which Affymetrix claims priority.[15] If this term is to have any written description support at all in the '365 patent specification, it is necessary to look to the '365 specification and interpret the claim term "housing" consistently with that description.

Several of the claims of the '365 patent refer to the "housing" as the location where a bar code is attached (*e.g.*, claims 1 and 2), and the only mention of a bar code in the specification is to a "top casing" being able to accommodate "labels or bar codes."

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Moreover, the term "housing" is defined by Webster's Dictionary as "something that covers or protects: as (a): a ***case*** or enclosure (as for a mechanical part of instrument) (b) a ***casing*** (as an enclosed bearing) in which a shaft revolves..." Ex. BB at 563 (*Merriam Webster's Collegiate Dictionary* (10th ed. 1994)). Thus, it is reasonable (and necessary) to look to the discussion of the term "casing," which is a term used in the specification, to inform the construction of the term "housing" in the claims.

[15] The term "housing" does appear in the Abstract for the '365 patent, but this Abstract was only added in an Amendment dated December 20, 2001 after claims to a "housing" were added.

The '365 specification. The figures and description in the '365 patent all illustrate the "casing" of the alleged invention to be something that separates the probe array from the surrounding atmosphere. Figures 4 and 5, for example, each show a casing that forms a cavity or chamber in which the probe array is located. In the various embodiments described, two or three casings (top, bottom and/or middle) are mated together by one of several techniques – welding, screws, glue, clips, etc. '365 col. 9:16-26. The casing thus forms a "***sealed*** thermostatically controlled chamber in which fluids can easily be introduced." '365 col. 2:8-9 (emphasis added). The "housing" of the invention thus "houses" or "encases" the probe array, forming a reaction chamber that is separated from the outside atmosphere.

The '365 prosecution history. Affymetrix distinguished at least one reference during prosecution on the basis that it did not disclose a "housing" as that term is used in the '365 patent. The Mitsuhashi prior art patent teaches a microtiter plate having a plurality of wells with different nucleic acid probes bound to a solid support (*e.g.*, beads) for hybridization. Affymetrix distinguished this prior art, arguing that "Mitsuhashi does not teach a housing including a fluid cavity for hybridization, as claimed in several pending claims." Ex. CC (App. No. 09/907,196 – 12/20/01 A't at 14). Thus, Affymetrix cannot now contend that a "housing" is merely a structure that contains something (like a microtiter well) — it must be construed to be a casing that separates the probes from the surrounding atmosphere.

Inventor testimony.

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This testimony is entirely consistent with the intrinsic evidence discussing this term, and Illumina's proposed construction for "housing" should be adopted.

2. "biological polymers immobilized on a surface/substrate"

Illumina's Construction	Affymetrix's Construction
two or more biological polymers of different sequence chemically linked to a single surface	two or more surface-immobilized biological polymers that are recognized by a particular target

The various permutations of the term "biological polymers immobilized on a surface/substrate" should all be construed consistently to require two or more biological polymers of different sequence that are chemically linked to a single surface. There are two sub-issues presented by this claim term – (1) what is meant by the term "immobilized," and (2) whether the polymers must be bound to a single surface or substrate.

As to the first sub-issue, immobilization of a biological polymer to a surface/substrate requires chemical attachment of the polymer. The definition of "probe" in the patent makes clear that it is the "molecule" itself that is immobilized on the surface. '365 col. 4:4-5. The only method disclosed in the patent for "immobilizing" the polymers on the surface/substrate is to have "linker molecules [ ] provided on a substrate" ('365 col. 4:50), and then synthesizing the polymers on the end of these linker molecules using Affymetrix's photolithographic technique. This photolithographic technique utilizes the concept of *in situ* synthesis, building the polymers one base (monomer) at a time "until polymers of a desired length and desired chemical sequence are obtained." '365 col. 5:2-3. By growing the polymers on linker molecules attached to the surface, all of them are thus chemically linked to the surface.

As to the second sub-issue, all of the asserted claims of the '365 patent include the claim language requiring an array of different probes of "biological polymers immobilized on" a singular object – "a first surface" (independent claims 1, 2), or "a substrate" (independent claims 7, 41), or "a surface" (independent claims 10, 47). All of the evidence in the '365 patent dictates a singular

construction of these terms – two or more biological polymers must be attached to a single surface/support. *See, e.g., N. Am. Vaccine, Inc. v. Am. Cyanamid Co.*, 7. F.3d 1571, 1575-76 (Fed. Cir. 1993) (construing "a" in the singular because the patent claims and specification disclosed only singular embodiments); *see also Insituform Tech., Inc. v. Cat Contracting, Inc.*, 99 F.3d 1098, 1105-06 (Fed. Cir. 1996) (construing "a cup" to require singular form, where claims referred to "a cup" and "the cup," and neither the specification nor figures disclosed the use of more than one cup).

First, the claims of the '365 patent dictate a singular construction. For example, claim 1 requires:

> . . . a substrate comprising a first surface including a probe array with different probes comprising biological polymers immobilized on said first surface; said probe array including a density exceeding 100 different biological polymers per cm^2 . . .

'365 col. 23:11-15. The "first surface" is a single surface on which there is a probe array. There is no second surface, let alone a second substrate. A singular construction is clearly dictated.

Second, the specification also dictates a singular construction. Essentially all of the asserted claims require a certain number of polymers within a specific density – *e.g.*, the "100 different biological polymers per cm^2" limitation of claim 1. The ***only*** support for these density limitations in the specification expressly confirms that the claims require a single substrate:

> In some embodiments ***a single substrate*** supports more than about 10 different monomer sequences and preferably more than about 100 different monomer sequences, although in some embodiments more than about 10^3, 10^4, 10^5, 10^6, 10^7, or 10^8 different sequences are provided on ***a*** substrate.

'365 col. 5:45-49 (emphasis added). The entirety of the specification, and all of the figures, likewise always refer to probe arrays of biological polymers being on a single "surface" or "substrate." *See, e.g.*, '365 Abstract ("The substrate has ***a first surface*** that includes an array of probes . . ."); col. 1:66-67 ("Methods and devices for packaging ***a*** substrate having an array of probes fabricated on ***its surface*** are disclosed.").

V. THE SOFTWARE PATENT

A. The '716 Patent

The '716 patent generally relates to a computer program that takes hybridization intensity data and makes determinations ("base calls") regarding the sequence of an unknown nucleic acid. The claims do not require any specific mathematical manipulations — all that is required is that two or more "probe intensities" be compared to each other and a base call is then made based on this comparison and the sequences of the probes. Independent claim 1 reads as follows:

> 1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:
>
> computer code that receives a plurality of signals corresponding to ***probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe*** with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;
>
> computer code that performs a ***comparison of said plurality of probe intensities to each other***;
>
> computer code that ***generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes***; and
>
> a computer readable medium that stores said computer codes.

'716 cols. 41:60-42:67 (emphasis added to highlight the disputed terms). Asserted independent claim 5 largely tracks claim 1, and asserted dependent claims 9 and 10 add the limitations of an array (claim 9) and fluorescent intensities (claim 10).

1. "probe"

Illumina's Construction	Affymetrix's Construction
a nucleic acid of known sequence that is capable of hybridizing to a complementary sequence of the unknown sample nucleic acid	a nucleic acid of known sequence that is capable of hybridizing to its complementary sequence

The term "probe" in the '716 patent should be construed to mean a nucleic acid of known sequence that is capable of hybridizing to a complementary sequence of the unknown sample

nucleic acid. The parties apparently agree that a "probe" is a nucleic acid of known sequence, but disagree as to what it is intended to hybridize with.

The asserted claims of the '716 patent all require a computer or system "that identifies an ***unknown base*** in a ***sample*** nucleic acid sequence." *See, e.g.*, '716 claims 1 and 5 (emphasis added). Illumina's construction simply reflects this "unknown sample nucleic acid sequence" into its construction. The specification likewise repeatedly refers to identifying an unknown base in a sample nucleic acid sequence, and states that "the sequences of interest may, for example, be normal or mutant portions of a gene, genes that identify heredity, or provide forensic information." '716 col. 4:64-67. There is no reference anywhere in the patent to a known probe sequence hybridizing with another known sequence or with anything that is not the biological sample being interrogated.

Despite no intrinsic support, Affymetrix's proposed construction allows for the probe to be complementary to another ***known*** sequence, such as in the context of hybridization of a "tag" or label sequence to its complement.[16] Not only is this construction inconsistent with the claim language and specification, but it is also inconsistent with Affymetrix's statements during prosecution. Affymetrix specifically distinguished prior art during prosecution that "uses a single probe which will hybridize to a ***tag*** on the nucleic acid ladder fragments," as contrasted with the '716 patent's "probe intensities that indicate the extent of hybridization of probes differing by a single base and the ***sample*** nucleic acid sequence." Ex. DD (App. No. 08/327,525 ("'525 App.") – 5/20/96 A't at 13-14). The term "probe" thus must be construed as proposed by Illumina to avoid the legal error of allowing Affymetrix to read the claim back on the "tag" prior art that Affymetrix stated during prosecution was not covered by the claims of the '716 patent. *See, e.g., Hockerson-Halberstadt*, 222 F.3d at 957.

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[16] **REDACTED**

2. "probe intensity"

Illumina's Construction	Affymetrix's Construction
intensity from a labeled sample nucleic acid hybridized to a probe location	a detectable signal, *e.g.*, fluorescence

The term probe intensity should be construed to be the intensity from a labeled sample nucleic acid hybridized to a probe location. This construction stays true to and reflects the intrinsic evidence, while Affymetrix's non-construction is an attempt to broaden the claims beyond that which was contemplated and described.

Figure 2C of the '716 patent, and the related discussion in the specification, informs the construction of the term "probe intensity." As depicted in Figure 2C (reproduced below), the probes are those sequences with "T" at the top, and "A" at the bottom, each with a different base at the fourth position down. The unknown sample is the sequence with "A" at the top and "T" at the bottom, which hybridizes (preferentially) to its complementary sequence. The unknown sample (highlighted below in Figure 2C) is labeled with some kind of marker – a "fluorescent reporter group" in the Figure – which is then detected.

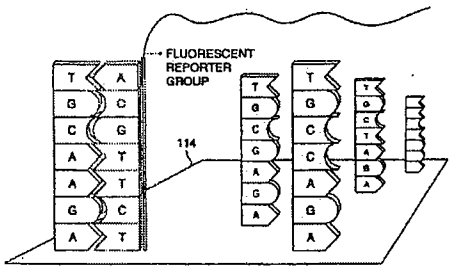

FIG. 2C

The "probe intensity" is thus the intensity from the probe location at which there is a labeled sample nucleic acid hybridized to the probe. The '716 patent specification confirms this construction:

> When a ***fluorescein-labeled (or otherwise marked) target*** ... is exposed to the array, it is complementary only to [one probe], and ***fluorescein will be primarily found on the surface of the chip where that probe is located***. Thus, for each set of probes that differ by only one base, the image file will contain four fluorescence intensities, one for each probe. Each fluorescence intensity can therefore be associated with the base of each probe

> that is different from the other probes.... By analyzing the [four] ***fluorescence intensities associated with a specific base location***, it becomes possible to extract sequence information from such arrays using the methods of the invention disclosed herein.

'716 cols. 6:60-7:7. The specification repeatedly refers to probe intensity as reflecting a probe with a labeled nucleic acid sequence hybridized to it. *See, e.g.*, '716 col. 3:34-36 ("The present invention provides methods of analyzing hybridization ***intensity*** files for a chip containing ***hybridized nucleic acid probes***."); col. 1:64-67 ("improved methods of analyzing fluorescent image files of a chip containing ***hybridized nucleic acid probes*** in order to call bases in sample nucleic acid sequences"); col. 1:44-47 ("A fluorescently ***labeled nucleic acid*** is then brought into contact with the chip and a scanner generates an image file indicating the locations where the labeled nucleic acids bound to the chip. Based upon the identities of the ***probes at the locations***. . ."). There is no mention anywhere in the specification of an intensity that is measured from anything but a labeled sample nucleic acid hybridized to a probe.

Statements made during the prosecution history confirm Illumina's proposed construction. Distinguishing prior art that used tags and enzymatic methods to enhance the hybridization signals, the '716 patent applicants confirmed that a probe intensity is an intensity from the location of a hybridized probe:

> In the present invention, the ***locations of the hybridized probes are known*** and, as such, the computer algorithms of Weiss and Stockham would indeed seem to teach away from the present invention which is directed to calling an unknown base according to ***the probe intensities from nucleic acid probes*** that differ by a single base.

Ex. DD ('525 App. – 5/20/96 A't at 14 (emphasis added)).

Affymetrix's construction ignores the concept of a ***probe*** intensity as described in the '716 patent, and instead seeks to encompass any signal no matter how or why it is generated. The correct construction of "probe intensity" must give meaning to the claim language used, as illustrated by the intrinsic evidence, to be an intensity from a labeled sample nucleic acid hybridized to a probe location.

3. "corresponding to probe intensities for a plurality of nucleic acid probes"

Illumina's Construction	Affymetrix's Construction
two or more probe locations each having one and only one probe intensity	relating to a detectable signal, *e.g.*, fluorescence, from two or more nucleic acid sequences of known sequence that are capable of hybridizing to a complementary sequence

The claim phrase "corresponding to probe intensities for a plurality of nucleic acid probes" should be construed to limit each probe location to have a single corresponding probe intensity.

There are admittedly two ways to read this limitation, either (1) that there are multiple probes each with one or more probe intensities, or (2) that each probe location has a single corresponding probe intensity. The answer to this question comes from the prosecution history, and Affymetrix's unequivocal clarification that each probe location would have one and only one probe intensity.

Referring to the application claims, the Examiner raised two questions as to these claims asking how a single probe could generate more than one intensity:

> Further the recitation of "each probe intensity of a probe" because ***it is unclear how a single probe can have more than one intensity*** (as implied by the use of the term "each").
>
> * * *
>
> Claims 13 and 14 are indefinite in reciting "Probe intensities of a probe" in that ***it is not clear how "a" probe generates more than one intensity.***

Ex. FF ('525 App. – 12/19/95 Office Action at 3-4 (emphasis added)). Affymetrix's response is telling – it did not explain that a single probe could have more than one intensity, but instead amended the claims to clarify that multiple "probes" each have their own "probe intensities":

> Also, the Examiner stated that "each probe intensity of a probe" is unclear. Claim 67 recites instead "each probe intensity of probes" (emphasis supplied). Accordingly, the rejection does not apply to the new claims.
>
> * * *
>
> In regard to claims 13 and 14, the Examiner stated that it is not clear how "a" probe generates more than one intensity. Claims 73 and 74 instead contain the plural "probes."

Ex. DD ('525 App. – 5/20/96 A't at 11). It is thus clear that, in the context of the '716 patent, any one probe location can only have a single probe intensity associated with it.

4. "indicating an extent of hybridization"

Illumina's Construction	Affymetrix's Construction
indicating the strength of binding so as to distinguish a single-base mismatch	relating to the relative binding of

The term "indicating an extent of hybridization" should be construed to mean indicating the strength of binding so as to distinguish a single-base mismatch. Again, Illumina seeks to actually construe the claim consistent with the intrinsic evidence, while Affymetrix wants an amorphous non-construction that will cast the jury adrift with confusion.

The '716 specification. Illumina's construction comes directly from the discussion of the concepts of probe intensities and what they indicate *vis-à-vis* hybridization in the specification. The "General" discussion section of the specification explains that higher probe intensities indicate stronger binding to the probes:

> Since higher photon counts will be observed where the labeled receptor has ***bound most strongly*** to the array of polymers . . .

'716 col. 4:43-45 (emphasis added). Likewise, a discussion of one of the specific embodiments confirms this construction of what is indicated by the probe intensities:

> If the fluorescently marked sample sequence is exposed to the above four mutation probes [each differing by a single base], the intensity should be highest for the probe that ***binds more strongly*** to the sample sequence.

'716 col. 7:59-62 (emphasis added). All of the embodiments of the asserted claims in the specification utilize four probes, each having a different base at the interrogation position, and then requiring a comparison of the intensities at the locations of these probes that differ by a single base. *See, e.g.*, '716 col. 7:55-58; col. 11:4-7; col. 11:11-13. Thus, to implement the invention as described, it is necessary to perform hybridizations so as to distinguish single-base mismatches from one another. *See Network*, 242 F.3d at 1352 ("The claims are directed to the invention that is

described in the specification; they do not have meaning removed from the context from which they arose.").

The '716 prosecution history. Illumina's construction is further confirmed by statements made by Affymetrix during prosecution of the '716 patent. Affymetrix distinguished prior art on the basis that its claimed invention required the probe intensities to indicate an extent of hybridization so as to discriminate single-base mismatches:

> Weiss and Stockman do not disclose or suggest inputting probe intensities to identify the unknown base ***where the probe intensities indicate the extent of hybridization of probes differing by a single base*** and the sample nucleic acid sequence.

Ex. DD ('525 App. – 5/20/96 A't at 13) (emphasis added). This representation was then relied upon by the Examiner in explaining his reasons for allowing the claims:

> Claims 60-105 are allowable over the prior art of record. The closest prior art of record is Weiss and Stockham who teach equations and formulas for sharpening signal peaks derived from electrophoretic migration patterns of nucleic acid ladders. Weiss and Stockham do not teach or fairly suggest a method if [sic] inputting probe intensities to identify an unknown base where the probe intensities ***indicate an extent of hybridization of probes differing by a single base*** and the same nucleic acid as recited in the base claim, claim 60.

Ex. GG ('525 App. – 7/9/96 Office Action at 5) (emphasis added). Thus, Affymetrix prevailed in obtaining its claims on the basis that its invention allowed one to discriminate between hybridization intensities from probes differing by a single base, and this concept must be reflected in the proper claim construction.

5. "comparison of said plurality of probe intensities to each other"

Illumina's Construction	Affymetrix's Construction
ranking of probe intensities from a hybridization experiment	an examination of the detectable signals of two or more probes in relation to each other

The claim limitation "comparison of said plurality of probe intensities to each other" should be construed to require a ranking of the probe intensities, as opposed to Affymetrix's construction that merely requires some metaphysical "examination" that inherently happens any

time you have two numbers. The key is that the probe intensities must be compared ***to each other***, not to some previously-generated reference or standard value(s).

The '716 specification. The specification repeatedly refers to the comparison between probe intensities as involving a determination of their rank relative to one another — *i.e.*, which is highest, second highest, etc. For example, in describing one embodiment, the specification explains that "the base intensities are sorted in descending order of intensity." '716 cols. 8:61-62; 9:50-54. Throughout the specification it talks about identifying the "highest intensity base" to then attempt to make the base call. *See, e.g.*, '716 cols. 9:1, 55; 12:66; 19:62. It follows that a base call cannot be made according to the probe with the highest intensity if the "comparing" step of the claims does not somehow identify what the highest intensity is by actively comparing the intensities to each other. Thus, some aspect of ranking of the intensities (determining which is greater than the other) must be included in the Court's claim construction.

The '716 prosecution history. The prosecution history is entirely consistent with Illumina's construction. Again, the Examiner questioned the '716 patent applicants as to the intended coverage of their proposed claims, and the claims were clarified in such a way as to dictate Illumina's construction and reject Affymetrix's. The Examiner made the following inquiry near the end of prosecution:

> Claim 60 is indefinite in the recitation of "comparing said plurality of probe intensities" in that it is not clear what the probe intensities are compared to (each other? a standard value?)

Ex. GG ('525 App. – 7/9/96 Office Action at 3-4). The '716 patent applicants then amended the claims to clarify that the probe intensities must be compared "to each other" – highlighting Figures 3, 4A and 5A for support — as opposed to a standard or other value. Ex. HH ('525 App. – 1/13/97 A't at 14). Thus, the comparison of probe intensities to each other requires an evaluation of them against one another to put them in rank order.

6. "generates a base call"

Illumina's Construction	Affymetrix's Construction
identifies a nucleotide as A, C, G or T (or U)[17]	determines which nucleotide is most likely to be present at a particular position in a nucleic acid sequence

The term "generates a base call" should be construed to require identification of a nucleotide as one of the four possible bases. The claims specifically require that a ***base*** call be made by the computer program, as opposed to simple identification of a genotype of a particular sample. All of the embodiments disclosed in the specification illustrate a base call being made of A, G, C, or T, or that no call is made.

The '716 patent prosecution history confirms this construction. Describing the invention during prosecution, the patent applicants stated that "after comparing the probe intensities, an unknown base is identified (typically as A, C, G or T) according to the results of the comparison." Ex. DD ('525 App. – 5/20/96 A't at 12).

Affymetrix has previously put forth Illumina's construction when it asserted the '716 patent in litigation in California:

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. It should not now be able to run away from its prior proposal to fit its infringement contentions in this case.

7. "generates a base call … according to the result of said comparison and sequences of said nucleic acid probes"

Illumina's Construction	Affymetrix's Construction
generates a base call as the base-pair complement to the probe with the highest probe intensity(ies)[18]	determining which nucleotide is most likely to be present at a particular position in a nucleic acid sequence

[17] When working with RNA, the base "U" replaces "T" in the four-base code discussed above for DNA.

The final disputed limitation requires that the computer program "generates a base call … according to the result of said comparison and sequences of said nucleic acid probes." This should be construed such that the base is called as the base-pair complement to the probe with the highest probe intensity. Affymetrix's construction ignores the claim language "according to the result of said comparison and sequences of said nucleic acid probes" and should be rejected.

The '716 specification. The patent specification describes that the base call is made by (1) identifying the probe location with the highest intensity, and then (2) calling the base as the complement (*i.e.*, A-T, or G-C) to the probe with this highest intensity. In the "General" section of the specification, the making of a base call according to these two points is discussed:

> Since ***higher photon counts*** will be observed where the labeled receptor has bound more strongly to the array of polymers [probes], and since the monomer sequence of the polymers [probes] on the substrate is known as a function of position, it becomes possible to determine the sequence(s) of polymers [probes] on the substrate that are ***complementary*** to the receptor.

'716 col. 4:43-49 (emphasis added). The specification further states:

> If the fluorescently marked sample sequence is exposed to the above four mutation probes, the intensity should be highest for the probe that binds most strongly to the sample sequence. Therefore, if the probe 3'-TTTGA shows the ***highest intensity***, the ***unknown base in the sample will generally be called*** an A mutation because the ***probes are complementary to the sample sequence***.

'716 col. 7:59-65 (emphasis added). The flowcharts depicting the invention similarly refer to "Call Base 1 Complement," confirming that the base is called as the complement to the probe with the highest intensity. '716 Figure 3.

The '716 prosecution history. The patent applicants, referring to the patent specification to address § 112 rejections, are on record that the base is called as the complement to the probe with the highest intensity:

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[18] There is the possibility that a base might be called as one of two or three bases – *e.g.* A and G – if the intensities are not statistically distinguishable from one another. In that case, the base will be called as the complement to the probes with the highest two (or three) intensities.

> Applicants respectfully submit that, when read in light of the specification as the case law requires, the claims are not unclear. Applicants' specification provides full detail on possible "comparing" and "generating" (as amended) steps. For example, the highest probe intensity may be compared to the next highest probe intensity to generate a ratio. If this ratio is greater than a predetermined ratio cutoff, the unknown base ***will be called according to (e.g. complementary to) a base in the probe with the highest probe intensity.***

Ex. HH ('525 App. – 1/13/97 A't at 14-15 (emphasis added)). Thus, the "according to" language in the claims was clearly intended to require the base call to be the complement to the probe with the highest probe intensity.

CONCLUSION

For the foregoing reasons, Illumina respectfully requests that the Court construe the disputed terms of the asserted claims of the Affymetrix patents-in-suit as set forth above.

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CERTIFICATE OF SERVICE

I hereby certify that on the 17th day of April, 2006, I caused to be electronically filed the foregoing document, **PUBLIC VERSION OF ILLUMINA, INC.'S OPENING MARKMAN BRIEF,** with the Clerk of the Court using CM/ECF which will send notification of such filing to the following:

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